**REVIEW:**

# Signet-ring cell carcinoma of colorectum – current perspectives and molecular biology

Running title: Colorectal signet-ring carcinoma

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**Abstract**

*PURPOSE*: Colorectal signet-ring cell carcinoma (SRCC) is rare and no detailed information of the molecular biology of the disease is available.

*METHODS:* The literature on the clinical, pathological, and in particular, the molecular biology of this rare entity was critically reviewed. The characteristics of 2 patients with colorectal SRCC with some unusual clinical features and distinctive molecular findings were also discussed.

*RESULTS*: Colorectal SRCC mostly occurs in younger patients, is larger and has different site predilection compared with conventional colorectal adenocarcinoma. It can occur as one of the synchronous cancers in the colorectum. The cancer is usually diagnosed at advanced stages because of the late manifestation of symptoms and aggressive treatment strategy is required Limited reports in the literature have shown that the variant of colorectal cancer demonstrated a different pattern of genetic alterations of common growth kinase related oncogenes (K-ras, B-raf), tumour suppressor genes (p53, p16), gene methylation and cell adhesion related genes related to the Wingless signalling pathway (E-cadherin and beta-catenin) from conventional colorectal adenocarcinoma. Colorectal SRCC also showed high expression of mucin related genes and genes related to the gastrointestinal system. There was also a higher prevalence of microsatellite instability-high tumours and low Cox-2 expression in colorectal SRCC as opposed to conventional adenocarcinoma.

*CONCLUSIONS*: Colorectal SRCC has unique molecular pathological features. The unique molecular profiles in SRCC may provide molecular based improvements to patient management in colorectal SRCC.

KEYWORDS: colorectal, signet-ring cell carcinoma, molecular biology

## INTRODUCTION

Signet-ring cell carcinoma (SRCC) is a rare type of adenocarcinoma characterised by mucin secreting cancer cells that contain intracytoplasmic mucin. The carcinoma can occur in many different sites of the body but the most common site is in the stomach. SRCC in colorectum is rare and the first case was reported by Laufman and Saphir in 1951 [1]. Because of its rarity, the characteristics of this tumour are seldom described in detail. Most of the reported cases in the literature are either case reports or small series. In addition, molecular characteristics are seldom mentioned. Thus, in this review, we presented the clinical and pathological features of 2 of our cases and reviewed the current perspectives of this entity.

## METHODS

A literature search was conducted using the PubMed database on topics related to SRCC. All full-text articles published in English were selected for review. The histological sections of all the colorectal cancer surgically removed in the 8- year period (2002-9) in the Department of Surgery, James Cook University were reviewed by the authors (VG and AL). The clinical and pathological data of the cancers were recorded in a database. Of the 443 colorectal cancers reviewed, 2 were SRCCs. A paraffin block was obtained from one case to perform immunohistochemical studies on molecular markers.

## CASE PRESENTATION

### Case 1.

A 73-year-old man underwent abdominal peritoneal resection for a cancer diagnosed on anal biopsy. His blood carcinoembryonic antigen (CEA) level was 1.3

ug/L (normal range < 5 ug/L). The cancer was 25mm in extent, located at the lower part of the rectum and involved the anus. The pathological diagnosis was a signet-ring cell carcinoma (Figure 1). At the time of resection, the pathological staging was T4N1 (stage 3). However, liver metastases were detected within a month after operation (stage 4). The patient died of the cancer 10 months after resection.

**Case 2**

A 76-year-old man underwent subtotal colectomy for synchronous carcinoma in the colon. He has slightly elevated CEA level before operation (30 ug/L). At operation, a signet-ring cell carcinoma which measured 50 mm in maximum extent was noted in the ascending colon. The pathological staging was T3N0 (stage 2). Other than this, the patient had 3 smaller cancers detected. These included a conventional moderately-differentiated adenocarcinoma (staging = T3N0, stage 2) in the transverse colon, a mucinous adenocarcinoma (staging = T2N0, stage 1) in the caecum and a well-differentiated adenocarcinoma (staging = T2N0, stage 1) also in the caecum. There were also a few hyperplastic polyps at the colon and a flat adenoma in the caecum. The patient had no recurrence and his CEA was within the normal limits after the operation. He died of a bleeding gastric ulcer 65 months after the operation.

Immunohistochemical studies on the signet ring cell carcinoma showed that the tumour displayed nuclear positivity for p21 protein and retinoblastoma protein. More than 90% of the cancer cells were positive for these proteins. On the other hand, the cancer cells were negative for p16, p53, hTERT and aurora kinase.

## DISCUSSION

### Epidemiology

The true prevalence of SRCC is difficult to be determined. In the larger series available, signet-ring cell carcinoma comprises approximately 0.1-2.6 % of colorectal cancers noted [2-7]. In our surgical series, SRCC comprised 0.45% of the primary resected colorectal cancer. It accounted for 0.4% (1 of 251) of colonic cancer and 0.5% (1 of 192) of rectal cancer.

In the literature, SRCC mostly occurs in younger age groups (≤ 40) than conventional colorectal adenocarcinoma and more often in females [2-7]. However, in our series, the 2 cases presented were elderly males. Also, SRCC is often present with more advanced stage lesions. The tumour is more common in proximal colon and case 2 in our series was noted in the caecum. In the rectum, SRCC is usually located in lower portions than conventional adenocarcinoma [8]. Case 1 in our series was located in this region and was first detected by anal biopsy.

According to findings in the USA, even though the incidence of colorectal adenocarcinoma is decreasing in recent years, the incidence of signet ring cell carcinoma is still stable [6]. Also, the incidence in Caucasians is higher than African Americans and other ethnic groups in the USA [6]. Colorectal SRCC is more common in patients who had a long standing history of inflammatory bowel diseases and history of irradiation [9-10].

### Clinical manifestations and diagnosis

One of the characteristic features of colorectal SRCC is the late manifestation of symptoms and many of them are diagnosed at advanced stages [11]. The

presentations of colorectal SRCC include rectal bleeding, small bowel obstruction, abdominal pain, bloody stool, abdominal mass, vomiting, constipation and abdominal fullness [5,12]. Delay in diagnosis reduces the chance of curative resection and increases the risk of local and distal metastasis [8]. Methods of diagnosis of colorectal SRCC do not differ from that of the conventional adenocarcinomas. In addition to the routine blood tests and radiological assessments, endoscopic biopsy is the common diagnostic technique for detecting the tumour in colorectum [11]. An emergency laparotomy may be the first diagnosis if the tumour is obstructing the colon and producing acute symptoms [12].

Crohn's disease in the colon mimics features of colorectal SRCC clinically [13]. Differentiating features for Crohn's disease include skipping longitudinal ulcer scar-like strictures, cobblestone appearance, segmental stricture, and pseudo-sacculations. Upper gastrointestinal endoscopy and barium enema are useful for clinical differentiation of colorectal SRCC from Crohn's disease. Also, in the presence of bilateral ovarian metastases, the main clinical differential diagnosis is whether the cancer arises from the stomach or the colorectum. Metastatic mucinous tumours of the female genital tract should also be differentiated from primary colorectal SRCC.

**Metastasis**

Compared with conventional colorectal adenocarcinomas, chance of metastasis is higher in SRCC [7]. The possible routes of metastasis are peritoneal, lymphatic and haematogenous. Metastasis to peritoneum is a common event in colorectal SRCC [4,12]. Anthony *et al* reported that peritoneal carcinomatosis is the most common pattern of treatment failure in SRCC [2]. Sites involved in

haematogenous metastasis of colorectal SRCC include, bone, liver, uterus, prostate lung and skin [5,7,14-17]. The most common sites of skin metastasis are abdominal wall and perineal area. An unusual presentation of colorectal SRCC with metastasis to upper lip has also been reported [17].

**Prognosis**

In general, the 5 year survival rate in larger series of colorectal SRCC range from 0-12% [3,5,18]. Disease recurrence is more frequent in colorectal SRCC compared to mucinous adenocarcinomas [18]. The reason for the poor prognosis may be the advanced tumour stage rather than the histology [8]. In our present series, one patient presented with advanced disease and the survival was less than a year. The other patient was detected at a less advanced stage and had long term survival even with synchronous cancers. It is likely the tumour staging is the best predictive factor for prognosis of colorectal SRCC.

In our previous study, which included colorectal mucinous adenocarcinoma and SRCC, it was found that factors like family history of colorectal cancer, and status of p53 and p16 expression may predict the prognosis [19]. However, only one case (case 2 in the present study) was pure SRCC and therefore more studies on the predictive effect of these factors in SRCC are required.

**Management**

Early diagnosis and aggressive treatment strategy is required for the management of primary colorectal SRCC [1-8]. Surgical management for SRCC is similar to conventional colorectal adenocarcinoma. Chemotherapy and radiotherapy were used as adjuvant therapies for advanced diseases.

## Pathology

### Macroscopic features

Tumour size of colorectal SRCC is usually larger when compared to conventional adenocarcinomas [8]. It has been reported that the most frequent presentation of SRCC is scirrhous appearance [7]. In addition, SRCC often had a mucoid appearance on macroscopic examination.

Synchronous cancer of the colorectum is uncommon. They are considerably clinically significant because the extra tumours may be missed and the high difficulty of preoperative diagnosis. Synchronous cancers are infrequently reported in SRCC [2,20]. Anthony *et al* have reported 14% (4 of 29) of patients with colorectal SRCC had synchronous cancers [2]. It is worth noting that case 2 in our series had 4 synchronous cancers. The smaller cancers had a more favourable pathological stage than the indexed SRCC. It may be due to the presence of multiple tumours that the patient's disease was detected at stage 2 in, contrast to many SRCC. In addition, one of the other cancers in this patient was a mucinous adenocarcinoma, the overall pattern of subtypes in this individual being highly unusual.

### Microscopic features

Signet ring-cell carcinoma is characterised by abundant intracytoplasmic mucin. Because of the presence of mucin, colorectal SRCC shows similarity with mucinous adenocarcinomas. There are some clinicopathological differences between these two cancers [19]. In SRCC, the abundant intracytoplasmic mucin pushes the centrally placed nucleus to the periphery, giving an appearance like a signet ring. SRCC can be defined by the presence of these cells at more than 50 percent of total

tumour cells with prominent intracytoplasmic mucin. Signet ring cancer cells can occur in mucin pools of mucinous adenocarcinoma or in a diffusely infiltrative process with a minimal extracellular mucin. In some colorectal cancers, a combination of conventional glandular, mucinous and signet-ring cell morphologies can co-exist in the same cancer (Figure 2). The other differential diagnoses of SRCC include metastases from other sites like the stomach. In addition, in small biopsies, the diagnosis may be missed because the signet ring cancer cells may be misinterpreted as foamy macrophages.

**Molecular basis of SRCC**

*BRAF* encodes a RAS-regulated kinase that mediates cell growth and malignant transformation pathway activation. A slightly lower prevalence of *K-ras* mutation has been reported in SRCC compared to conventional adenocarcinomas [20-24]. Also, Wistuba and colleagues detected a mutation at codon 61 in 4 of the 16 cases of colorectal SRCC that was not present in conventional adenocarcinoma [22]. In addition, a comparison study of 9 colorectal SRCCs with 348 conventional colorectal adenocarcinomas revealed a higher frequency of BRAF mutation in colorectal SRCC (22% versus 8.6%) [24]. Thus, SRCC may have a distinct mutation pattern with respect to the main growth kinase pathways.

*p53* and *p16* are tumour suppressor genes that are implicated in the development and progression of many cancers. In our case 2, p53 and p16 protein expression was negative. On the other hand, in our previous study, we noted some of the signet ring tumour cells in mucinous adenocarcinoma were positive for p53 and p16 protein expression [19]. The loss of p16 protein expression in our study was in concurrence with the study by Ogino and colleagues who found loss of p16 protein

expression in 25% (1 of 4) of colorectal SRCC [24]. Mai, *et al* reported positive p53 immunohistochemical expression in 13 of the 15 colorectal SRCC in their study. It was shown that p53 protein expression was usually stronger in the adenocarcinoma component rather than the signet ring carcinoma component of the tumour [25]. In another study, 29% (2 of 9 cases) of SRCC were positive for p53 protein expression [23]. In addition, Wistuba and colleagues reported a lower level of p53 protein expression (40%; 4 of 10) in colorectal SRCC than in conventional colorectal adenocarcinoma [22]. However, Ogino and colleagues have reported p53 protein expression in 75% (3 of 4) of SRCC [24]. This illustrates the difficulty in obtaining reliable molecular data for colorectal SRCC, as all these studies have relatively small numbers of cases and no definite conclusions can be drawn.

*HATH1*, *MUC2* and *SOX2* are genes for regulation and production of mucin in the gastrointestinal tract. Park and colleagues studied the expression of the proteins for these genes in 7 cases of colorectal SRCC [26-27]. These proteins were frequently expressed in SRCC but rarely expressed in conventional adenocarcinoma. The findings suggested that mucin related genes were important in the pathogenesis of colorectal SRCC. Sentani *et al* reported expression of the mucin related proteins, MUC2 (80%) and MUC5AC (38%, 6 of 16) in colorectal SRCC in results similar to those of Park *et al* [26-28].

Sentani *et al* reported immunochemical expression of Reg IV and Claudin 18 in 16 cases of colorectal SRCC. They noted Reg IV in 100% (16 of 16) and Claudin 18 in 38% (6 of 16) of colorectal SRCC [28]. Both are cancer related genes of the gastrointestinal system and have been seen in SRCC in sites other than colorectum. They have been implicated in the carcinogenesis of SRCC, though additional studies are needed to determine precisely what their role may be.

Cytosine methylation leads to inactivation of genes when their promoter regions have CpG islands. In cancers cytosine methylation is commonly found on various tumour suppressor genes. Ogino *et al* reported relatively higher frequency of CpG island methylator phenotype (CIMP) in colorectal SRCC (33%, 2 of 6 cases) when compared to conventional adenocarcinoma (12%, 34 of 286) as detected by quantitative real time PCR [29]. This indicates that promoter methylation may play a significant role in the regulation of genes influencing the carcinogenesis or differentiation of colorectal SRCC.

E-cadherin plays a crucial role in cell to cell adhesion and maintaining epithelial morphology. Reduction of expression of E-cadherin due to aberrant hypermethylation is an important event for metastases in cancer. Loss of protein expression of E-cadherin has been reported in 100% (4 of 4) cases of colorectal SRCC [30]. This loss of protein expression may contribute to the high grade and invasive nature of SRCC in colorectum. In addition, strong expression of methyl CpG binding protein (MeCP2) was detected in these 4 cases by in-situ hybridization. Furthermore, 75% (3 of 4) of these cases had methylation of the *E-cadherin* promoter region detected by methylation-specific PCR. This implies the regulation of *E-cadherin* gene expression in colorectal SRCC is strongly influenced promoter methylation, reinforcing the importance of the role of CIMP in the disease.

Klarskov *et al* showed in a case of paired colorectal SRCC that the intramucosal, intraepithelial and stromal lesion cells of the cancer had a normal membranous expression of beta-catenin and E-cadherin [20]. Submucosally infiltrating cells, however, featured alterations to this pattern with loss of membranous expression of both proteins and nuclear accumulation of beta-catenin. Klarskov *et al* suggested that a disruption of the Wingless signalling pathway takes place at the

transition from the intramucosal to the submucosal level [20]. Conversely, however, the study by Wong *et al* noted aberrant beta catenin localization in 2 of 18 colorectal SRCC and concluded that there is no prominent role of the pathway in the colorectal SRCC [31]. Case series with higher numbers of invasive and high stage colorectal SRCC will be needed to fully determine the significance of these changes.

Microsatellite instability (MSI) is caused by inactivation of a group of genes responsible for DNA mismatch repair. It is a major mechanism for pathogenesis of colorectal cancer. The study by Witsuba *et al* on 10 SRCC cases showed that 3 cases (30%) were MSI-high tumours. In the same study, conventional adenocarcinoma showed slightly lower prevalence of MSI-high tumours (3 of 18; 17%) [22]. A separate study of 8 cases of colorectal SRCC showed 25% (n=2) were MSI-high tumours whereas 11% (38 of 351) conventional adenocarcinoma were MSI-high tumours [24]. These studies are small, but show good agreement of data, suggesting that colorectal SRCC are more likely to be MSI-high tumours than conventional adenocarcinoma.

COX-2 protein catalyses the conversion of arachidonic acid to prostaglandins and is related to the genesis and maintenance of colorectal cancers. Karnes *et al* found reduced immunohistostaining of COX-2 in 5 cases of colorectal SRCC compared to other colorectal cancer subtypes [32]. COX-2 expression in this study was also significantly correlated with colorectal carcinomas showing signs of defective DNA repair mechanisms. These findings indicate that colorectal SRCC may commonly feature defective DNA repair mechanisms, in relation to its higher rates of MSI. This general reduction in DNA repair capacity may be the source of colorectal SRCCs poor prognosis, or a component in a series of similar characteristics.

In our current study, we also presented for the first time the results of aurora kinase, hTERT, p21 and retinoblastoma protein (RB) expression in a case of SRCC. Aurora kinase is a regulator of mitosis. In our previous study, it was noted that colorectal mucinous adenocarcinoma were less often positive for aurora kinase than conventional adenocarcinoma [33]. The absence of expression of aurora kinase in Case 2 was in concurrence with the fact that aurora kinase expression was often lost in high grade cancers like SRCC. p21 protein is a downstream effector of the p53-specific pathway. In our previous study, p21 protein was shown to be lost or expressed at a lower level in non-mucinous colorectal carcinoma [34]. In this study, the high level of expression of p21 protein in SRCC shows a marked difference from non-mucinous colorectal carcinoma.

hTERT expression may reflect the telomerase activity in a cancer. It is worth noting that hTERT expression by endogenous p53 was demonstrated to be indirect and mediated by p21 and RB/E2F pathways in cancer cell lines [35]. RB is a tumour suppressor that is commonly expressed in colorectal cancer [36]. In our previous study, we noted hTERT protein expression in 63% of colorectal adenocarcinoma [34]. High levels of expression were noted in patients with metastases. Case 2 of the SRCCs in our series showed negative expression of hTERT and high level of expression of RB proteins. It is difficult to draw conclusions from the findings in one case. However, the SRCC in case 2 was at stage 2 and may account for the lack of hTERT protein staining.

**Conclusions**

In summary, SRCC occurs in younger age groups and more distant portions of the colorectum than conventional adenocarcinoma. Clinically, SRCC presents later,

with more advanced stages and with higher incidence of metastases, including to the peritoneum, than conventional colorectal adenocarcinoma. Limited reports in the literature have shown that this variant of colorectal cancer demonstrated a different pattern of genetic alterations from conventional colorectal adenocarcinoma. In the category of oncogenes and tumour suppressors, SRCC showed a lower prevalence of *K-ras* mutation, higher prevalence of *B-raf* mutation and lower prevalence of expression of p16 and p53 proteins than conventional colorectal adenocarcinoma. SRCC also showed higher CIMP (CpG island methylation for controlling gene expression) than conventional colorectal adenocarcinoma. In addition, colorectal SRCC also showed high expression of mucin related genes and genes related to the gastrointestinal system. There was also a higher prevalence of microsatellite instability-high tumours and reduced Cox-2 expression in colorectal SRCC compared to conventional adenocarcinoma. Thus, the overall clinical and molecular differences between these two groups support the notion that colorectal SRCC is an independent disease subtype.

The molecular studies in colorectal SRCC are hampered by the low incidence of SRCC and thus the low availability of tissue for study. Because of this, several studies have shown conflicting or ambiguous results, strongly demonstrating the need for larger series to improve our understanding of the pathogenesis of this cancer subtype. Trends, however, have begun to emerge from the molecular studies, in particular related to the loss of DNA repair mechanisms. These trends will inform future research into SRCC and may provide the first molecular based improvements to patient management in colorectal SRCC.

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**Figure Legends**

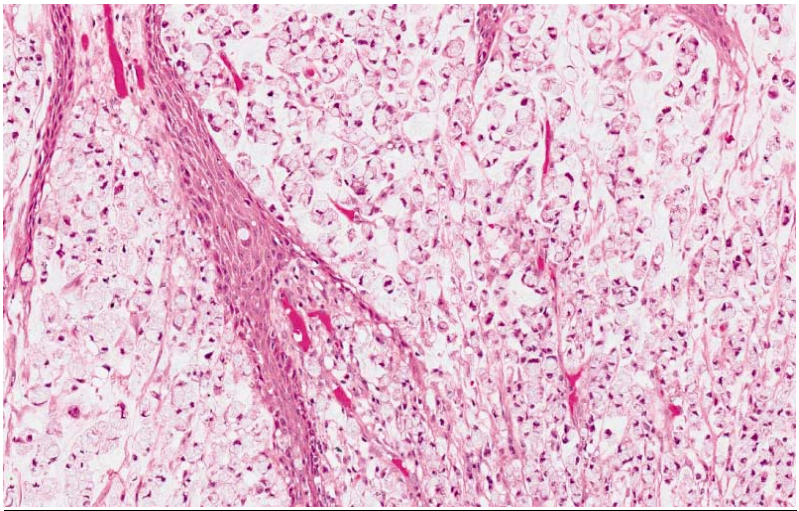

Figure 1

Microscopic section showing a rectal SRCC with signet ring cancer cells involved the anus.

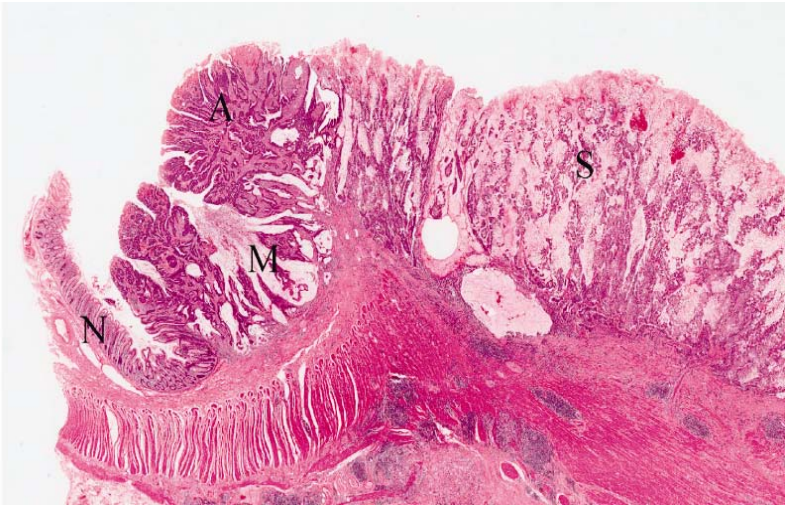


Figure 2

Microscopic section showing the co-existence of different patterns of cancer cells in colorectal cancer. N: non-neoplastic tissue; A:conventional adenocarcinomatous area; M: mucinous adenocarcinomatous area; S: signet-ring cancer region.